

Cycloreversions of Anions from Tetrahydrofurans. A Convenient Synthesis of Lithium Enolates of Aldehydes¹

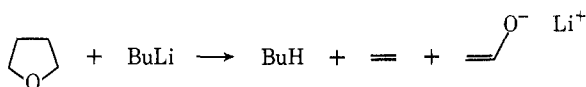
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Tetrahydrofuran (THF), 3,4-dialkyltetrahydrofurans, and 3,3,4,4-tetraalkyltetrahydrofurans are cleaved smoothly by *n*-butyllithium in hexane yielding alkenes and lithium enolates of aldehydes. The reactions appear to proceed by abstraction of an α hydrogen followed by $-\left[\pi_4s + \pi_2s\right]$ cycloreversion. In the case of THF itself, evidence was obtained for an 8% buildup of the α -metalated THF intermediate.

During lithiations with *n*-butyllithium in tetrahydrofuran (THF) at room temperature, we noted that, in cases in which the substrate metalates slowly, butyllithium cleaves THF smoothly to give butane, ethylene, and the lithium enolate of acetaldehyde. This type of



reaction has been reported previously² but not extensively studied. Because of the possibility that this reaction would provide the most convenient route to certain enolates (aldol condensation and polymerization can complicate the reaction of an aldehyde with base, but, in this cleavage route, *aldehyde is never present*), we decided to look further at the scope and mechanism of this reaction.

Experimental Section

Nmr spectra were recorded on Varian A-60 and HA-100 spectrometers; coupling constants are reported in hertz. Mass spectra were measured with a Hitachi Perkin-Elmer RMU-6E double-focusing spectrometer. Melting points are uncorrected.

3,4-Dimethyltetrahydrofuran.—A 2.3-g (0.016 mol) sample of 2,3-dimethylsuccinic acid (Aldrich Chemical Co.) was placed in a Soxhlet cup and the Soxhlet extractor was mounted above a three-necked flask containing 0.9 g (0.023 mol) of LiAlH₄ and 100 ml of ether. The ether was refluxed until all of the diacid had dissolved. The reaction flask was cooled to 0° and H₂O (6 ml) was added slowly with stirring. The ether solution was decanted and then used to extract the solid residue for 24 hr in a Soxhlet apparatus. The solvent was removed by distillation at atmospheric pressure, and 85% H₃PO₄ (0.2 ml) was added. After the mixture was refluxed for 2 hr, the material boiling below 100° was distilled out and dried by running a pentane solution of it through a short alumina column (basic, activity I). Removal of the bulk of the pentane by distillation gave 3,4-dimethyltetrahydrofuran³ (0.5 g, 30%).

2,2,3,3-Tetramethylbutane-1,4-diol.—A solution of 0.49 g (0.0031 mol) of tetramethylsuccinic anhydride⁴ in 3 ml of THF

(1) Taken in part from the Ph.D. thesis of D. E. P., 1969, and the M.S. thesis of L. M. K., 1970.

(2) (a) R. L. Letsinger and D. F. Pollart, *J. Amer. Chem. Soc.*, **78**, 6079 (1956), cleaved 2-phenyltetrahydrofuran with propylsodium and after work-up obtained (among other products) propane, ethylene, and acetophenone. (b) A. Rembaum, S. P. Siao, and N. Indictor, *J. Polym. Sci.*, **56**, 517 (1962), reported that ethyllithium decomposed in THF at 25° to give, among other products, ethylene and the lithium enolate of acetaldehyde. (c) Gilman and coworkers [H. Gilman and G. L. Schwabke, *J. Organometal. Chem.*, **4**, 483 (1965), and references cited therein] have measured the rates of decomposition of many organolithium compounds, including *n*-butyllithium, in THF, but do not report the products in the cases of present interest. (d) S. C. Honeycutt, *ibid.*, **29**, 1 (1971), has recently reported a kinetic study of the cleavage of THF by *n*-butyllithium.

(3) This material, like the starting acid, must be a mixture of *dl* and *meso* forms. For earlier preparations of mixtures of these stereoisomers by different methods, see Yu. K. Yur'ev and G. Ya. Kondrat'eva, *Zh. Obshch. Khim.*, **24**, 1645 (1954), and G. A. Razuvaev and L. S. Boguslavskaya, *ibid.*, **32**, 2320 (1962).

(4) A. F. Bickel and W. A. Waters, *Recl. Trav. Chim. Pays-Bas*, **69**, 312 (1950).


was added to a stirred solution of 1 g of lithium aluminum hydride in 100 ml of THF. After 16 hr at reflux, 1 ml of water, 1 ml of 15% NaOH, and 3 ml of water were added dropwise. The liquid was decanted and the solids were rinsed with ether. Evaporation gave crude diol, which on recrystallization from 60–90° petroleum ether gave 0.21 g (47%) of 2,2,3,3-tetramethylbutane-1,4-diol: mp 210–212° (sealed capillary; reported⁵ 224°); nmr (DCCl₃) τ 4.7 (broad s, 2), 6.7 (s, 4), and 9.1 (s, 12).

3,3,4,4-Tetramethyltetrahydrofuran.—In a sublimation apparatus, a solution of 0.22 g of the above diol in 1.3 ml of redistilled dimethyl sulfoxide was heated for 16 hr at 160°. The sublimate was resublimed at 100° to give 0.082 g (42%) of 3,3,4,4-tetramethyltetrahydrofuran: mp 106–107°; nmr (DC-Cl₃) τ 6.4 (s, 4), 9.1 (s, 12); mass spectrum 56 (base) and 128 (parent).

Reaction of Tetrahydrofurans with *n*-Butyllithium.—The tetrahydrofurans were dried over 4A molecular sieves activated by heating at 210° for 8 hr. A 0.012-mol sample was placed in an nmr tube. After cooling in a Dry Ice-isopropyl alcohol bath, *n*-butyllithium (Foote Mineral Co., 0.5 ml, 0.0008 mol) in hexane was added and the tube was sealed. The reactants were mixed thoroughly by shaking, and the tube was placed in an nmr probe at 35° for analysis at various time intervals. Sources of the tetrahydrofurans, their half-lives, and the products found are listed in Table I.

The various products were identified most conveniently by their nmr properties, especially ethylene, τ 4.7 (s, 4); propyl-

TABLE I
HALF-LIVES FOR CLEAVAGES AT 35°

Ether	Registry no.	$t_{1/2}$ for α cleavage, min	$t_{1/2}$ for β cleavage, min
Tetrahydrofuran ^a	109-99-9	10	
3-Methyltetrahydrofuran ^b	13423-15-9	50 ^f	
3,4-Dimethyltetrahydrofuran ^c	32970-37-9	70	
3,3,4,4-Tetramethyltetrahydrofuran ^c	32970-38-0	15 (at 80°)	
2-Methyltetrahydrofuran ^d	96-47-9	130 ^e	70 ^h
2,2-Dimethyltetrahydrofuran ^e	1003-17-4	>3000	700 ^h
2,5-Dimethyltetrahydrofuran ^b	1003-38-9	>3000	700 ^h
 Oxepane ^e	279-49-2	10	
	592-90-5		350

^a Mallinckrodt Chemical Works. ^b Aldrich Chemical Co. ^c See Experimental Section. ^d Eastman Organic Chemicals. ^e Chemical Samples Co. ^f Nearly equal amounts of the two sets of α -cleavage products (propylene, the enolate of acetaldehyde; ethylene, the enolate of propionaldehyde) were observed. ^g The only observed α -cleavage products were the enolate of acetaldehyde and propylene. ^h β cleavage involves only β protons external to the ring (*i.e.*, in the methyl groups) in these cases.

(5) M. F. Ansell, W. J. Hickenbottom, and P. G. Holton, *J. Chem. Soc.*, 349 (1955).

(6) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963).

ene, vinyl pattern at τ 4.4, 5.1, and 5.2; the enolate of acetaldehyde τ 3.08 (1, q, H₂), 6.85 (1, q, H_{3c}), 6.4 (1, q, H_{3t}), $J_{23c} = 5.4$, $J_{23t} = 13.4$, $J_{3c3t} = 2.0$ Hz; the enolate of propionaldehyde, τ 3.30 (1, d, H₂), 6.3 (1, m, H_{3t}), $J_{23} = 11.5$; the enolate of isobutyraldehyde, τ 3.44 (1, s, H₂), 8.44 (3, s, CH₃), 8.51 (3, s, CH₃). Ethylene was also characterized by its ir and mass spectra. Further evidence for the presence of the enolate of acetaldehyde was obtained by adding its THF solution dropwise to an aqueous solution with vigorous stirring at 0°; distillation gave acetaldehyde (ir, nmr).

Reaction of Oxepane with *n*-Butyllithium.—Oxepane was β cleaved smoothly under the above conditions to give the lithium salt of 5-hexen-1-ol, characterized by nmr absorption for the vinyl group at \sim 4.18 (1, m), 4.98 (1, d, $J = 16$ Hz), and 5.12 (1, d, $J = 10$ Hz), and for the methylene next to oxygen at 5.48 (2, m).

Reaction of 2,5-Dihydrofuran with *n*-Butyllithium.—2,5-Dihydrofuran (Aldrich Chemical Co.) cleaved rapidly under the above conditions to give the sickle isomer I of the enolate of crotonaldehyde: nmr τ 3.26 (1, m, H₄), 3.30 (1, d, H₂), 5.42 (1, q, H₃), 5.48 (1, q, H_{3t}), 5.75 (1, q, H_{3c}), $J_{23} = 6$, $J_{34} = 10.5$, $J_{45t} = 17$, $J_{45c} = 10.5$, $J_{3c3t} = 2$ Hz.⁷ After heating to 150° in a sealed tube, the nmr was unchanged.

Evidence for α -Lithiotetrahydrofuran.—A kinetic study of the THF cleavage was carried out in an nmr tube in the nmr probe at 35°. The decrease in butyllithium absorption at τ 11 and the increase in lithium enolate absorption at τ 3.1 were observed at 20 intervals over a period of 1 hr. The curves obtained were matched as well as possible using an analog computer and the assumption of the system



(A = butyllithium, C = enolate). The resulting rate constants were $k_1 = 1 \times 10^{-3}$ sec⁻¹ and $k_2 = 6 \times 10^{-3}$ sec⁻¹; the curves suggest an intermediate substance B which builds to a maximum concentration of 10% after 4 min.

A similar reaction was quenched with D₂O after 4 min. The extra height of the mass spectral peak at m/e 73 as compared to a standard from quenching with H₂O suggested that lithiotetrahydrofuran had been present in 8% yield.

Lithium Enolate of Acetaldehyde-³/₂Tetrahydrofuran.—A mixture of THF (1.0 ml, 0.012 mol) and *n*-butyllithium (4.0 ml, 0.0064 mol) in hexane was allowed to stand at room temperature for 6 days. The liquid was decanted, and the crystals were washed several times with hexane and then dissolved in THF-*d*₆; integration of the nmr spectrum showed THF and enolate in a 1.5 molar ratio.⁸ The crystals decomposed when exposed to the atmosphere for a few seconds.

Discussion

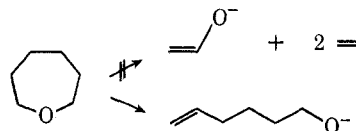
Scope.—As indicated by the first four entries in Table I, it appears that " α cleavage" to an olefin and the enolate of an aldehyde goes smoothly and quantitatively on tetrahydrofurans bearing no α substituents. After the cleavage of THF, the resulting lithium enolate solution is stable for at least 6 months. If desired, the ethylene (and butane) can be removed without affecting the lithium enolate by heating at 40° for several hours while passing nitrogen over the solution. The unsymmetrical example, 3-methyltetrahydrofuran, cleaved about equally in each direction, suggesting that only with symmetrical tetrahydrofurans will useful enolate syntheses be observed. The slowing effect of alkyl groups observed in this series is presumably due largely to the decreasing polarity of the solvent; the THF is present in large excess and serves as the principal solvent as well as a reactant.

The next three entries in Table I show that, with an α -methyl substituent, " β cleavage," involving ab-

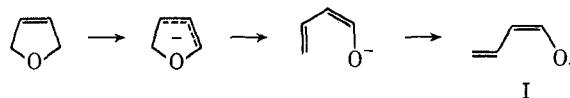
straction of a β proton from a methyl group, becomes the predominant reaction. α cleavage is appreciably slowed; it was observed only in the case of 2-methyltetrahydrofuran, whose α cleavage to the enolate of acetaldehyde and propylene rather than the enolate of propionaldehyde and ethylene can be rationalized on the basis that the more stable carbanion intermediate was involved.

The α cleavage observed for 7-oxabicyclo[2.2.1]heptane is probably fast for the same reason that bridgehead protons in bicyclic sulfides have been found to be more readily exchanged in base than the corresponding protons in acyclic sulfides.⁹

In none of the tetrahydrofurans was β cleavage involving abstraction of a ring hydrogen observed. This is probably because the geometry is so unfavorable for an E2 reaction in these five-membered ring compounds. Tetrahydropyran and oxepane were also reacted under these conditions; the products from the former are unknown, but the latter β cleaved smoothly with abstraction of a β hydrogen *in the ring*. With a ring as large as seven membered, the geometry required for an E2 reaction of this sort is apparently accessible.



Under these conditions, 2,5-dihydrofuran reacts vigorously to give an electrocyclic ring-opening product, the sickle-shaped dienolate ion I. This reaction has been reported by Kloosterziel and van Drunen⁷ to occur with potassium amide in liquid ammonia. By heating in a sealed tube at 150° we were unable to convert I to the W-shaped ion,⁷ indicating a barrier to rotation about the 2,3 bond of at least 23 kcal/mol.



Mechanism.—Letsinger and Pollart^{2a} noted that 2-phenyltetrahydrofuran cleaves much faster than THF itself and deduced that the first step was α -proton abstraction to give an anion, as shown below. In an effort to detect such an intermediate from THF, we ran a cleavage in an nmr tube at 35°. Although no signals were detected due to an intermediate, a plot of decreasing butyllithium concentration and increasing enolate concentration *vs.* time showed that at least one intermediate was involved and that it achieved its maximum concentration of about 10% after 4 min. When the reaction was quenched with D₂O after 4 min, the resulting THF was shown by mass spectral analysis to contain monodeuteriotetrahydrofuran in the amount expected if an 8% yield (based on BuLi) of THF anion had been present. This result contrasts with the failure to gain evidence for an intermediate in the related cleavages of dioxolanes and 1,3-dithiolanes;¹⁰ in those cases, cleavage is probably faster because negative

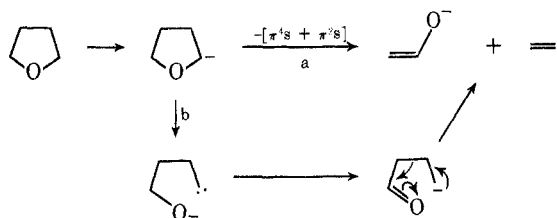
(7) H. Kloosterziel, J. A. van Drunen, and P. Galama, *Chem. Commun.* 885 (1969), report similar values for the potassium salt in NH₃ at -60°.

(8) We are indebted to Dr. S. Brenner for this result.

(9) S. Oae, W. Tagaki, and A. Ohno, *J. Amer. Chem. Soc.*, **83**, 5036 (1961).

(10) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969), and references cited therein.

charge develops in the transition state on *two* electronegative atoms rather than one.



In certain reactions of epoxides with strong bases, α -proton abstraction is apparently followed by carbon-oxygen bond cleavage to a carbene, which gives rise to several products.¹¹ A carbene path in the current cleavages (path b above) is ruled out, at least in the 2-methyl- and 2-phenyltetrahydrofuran^{2a} cases, by the cleavage products obtained; *e.g.*, the former gives propylene and the enolate of acetaldehyde rather than ethylene and the enolate of acetone. Relief of ring strain in the epoxide cases presumably aids considerably in the formation of the high-energy carbene intermediates.

(11) J. K. Crandall and L. H. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4526 (1967), and references cited therein.

The exclusion of path b leaves the much simpler, symmetry-allowed¹² $-\pi^4_s + \pi^2_s$ cycloreversion path as most likely for these reactions. Honeycutt's finding^{2d} that the rate of disappearance of butyllithium in THF is first order in butyllithium and 2.5 order in THF is understandable in terms of this mechanism, assuming 1.5 mol of THF on the average are necessary to solvate the lithium ions in the first step. In this connection, by increasing the butyllithium-THF ratio in a THF cleavage, we obtained a highly crystalline air-sensitive substance which appears to be lithium enolate of acetaldehyde $\cdot \frac{3}{2}$ tetrahydrofuran.⁸

Registry No.—2,2,3,3-Tetramethylbutane-1,4-diol, 10519-69-4; lithium enolate of acetaldehyde, 2180-63-4; lithium enolate of propionaldehyde, 33020-96-1; lithium enolate of isobutyraldehyde, 32970-42-6; lithium enolate of crotonaldehyde, 32970-43-7.

Acknowledgment.—We are grateful to the Petroleum Research Fund, Ethyl Corporation, and National Science Foundation for financial support.

(12) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

The Crystal and Molecular Structure of 5'-Demethoxy- β -peltatin A Methyl Ether¹

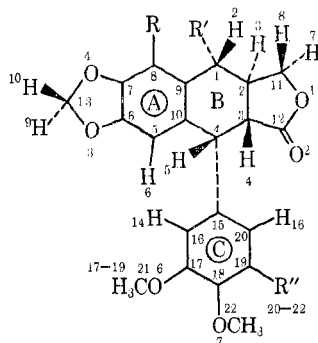
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The constitution and relative configurations proposed for this natural antitumor agent by Bianchi, Sheth, and Cole were confirmed by an X-ray study on the polymorph with mp 142–143°, and the conformation was revealed for the first time. The C ring is rotated so that a methoxyl group lies above the A ring. The carbons in the methoxyls on the C ring lie in the plane of the C ring, as far from one another as possible. The carbon in the methoxyl attached to ring A is nearly as far from the plane of the A ring as possible, on the same side as the C ring. An attempt to confirm the absolute configuration using anomalous scattering by oxygen gave inconclusive results but seemed to favor the configuration opposite to that proposed earlier. The structure was solved by symbolic addition and refined to an *R* of 0.039.

Although the antitumor activity of podophyllotoxin (I) and several related lignans has long been known,²



	R	R'	R''
I	H	OH	OCH ₃
II	⁵ 14 ¹¹⁻¹³ OCH ₃	¹ H	¹⁵ H
III	OCH ₃	H	OCH ₃

(1) This paper is based in part on the Ph.D. thesis of J. B. W., University of Arizona, 1971; some of the results were presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, ORGN 71.

(2) M. Belkin, *Proc. Soc. Exp. Biol. Med.*, **6**, 308 (1947); J. L. Hartwell and M. J. Shear, *Cancer Res.*, **7**, 716 (1947); M. G. Kelly and J. L. Hartwell, *J. Nat. Cancer Inst.*, **14**, 987 (1954).

no X-ray or other study showing their preferred conformation has been reported. 5'-Demethoxy- β -peltatin A methyl ether (II), one of the most active of these lignans, was recently isolated from a Mexican plant, *Bursera fagaroides*, and characterized by spectral comparisons with β -peltatin A methyl ether (III).³ As a check on the proposed constitution and configurations, and to learn the conformational preferences of a lignan of this series, we undertook an X-ray study on this substance.

Experimental Section

Collection and Reduction of the Data.—A clear needle of dimensions 0.2 × 0.2 × 0.7 mm of 5'-demethoxy- β -peltatin A methyl ether (II), mp 142–143°, was mounted for rotation about the needle axis (*c*). Oscillation and Weissenberg photographs indicated space group $P2_12_1$ or $P2_12_12_1$; the former was later established by the full intensity data. The crystal was mounted on a Picker FACS-1 four-circle automated diffractometer set for graphite-monochromatized Cu K α radiation, $\lambda = 1.54051 \text{ \AA}$. Unit cell dimensions, determined by least-squares refinement of the angular settings of seven reflections, were $a = 9.174 (3)$, $b = 27.628 (7)$, and $c = 7.620 (1) \text{ \AA}$.

For data collection, the 2θ scan technique using a basic 2° scan width modified for radiation dispersion was employed. After scanning at 2°/min, 10-sec background counts were taken at both ends of the scan. Three standard reflections were

(3) E. Bianchi, K. Sheth, and J. R. Cole, *Tetrahedron Lett.*, 2759 (1969).